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DICTIONARY FILE UPDATES:  19 AUG 2008  HIGHEST RN 1042061-07-3

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http://www.cas.org/support/stngen/stndoc/properties.html

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L1      STRUCTURE UPLOADED

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L1              STR
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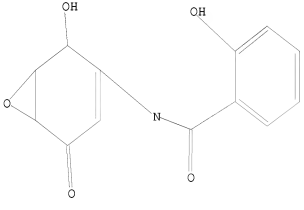


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Structure attributes must be viewed using STN Express query preparation.


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FULL SCREEN SEARCH COMPLETED -      422 TO ITERATE

100.0% PROCESSED      422 ITERATIONS                                 8 ANSWERS
SEARCH TIME: 00.00.01

L2            8 SEA SSS FUL L1
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COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                       178.36     178.57

FILE 'CAPLUS' ENTERED AT 12:24:16 ON 20 AUG 2008
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FILE COVERS 1907 - 20 Aug 2008  VOL 149 ISS 8
FILE LAST UPDATED: 19 Aug 2008  (20080819/ED)

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reclassification data for the second quarter of 2008.

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http://www.cas.org/legal/infopolicy.html

=> l2
L3          56 L2

=> l3 and py<2005
     25112822 PY<2005
L4          21 L3 AND PY<2005

=> d l4 ibib abs 1-21 hitstr

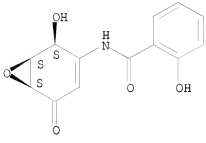
L4   ANSWER 1 OF 21  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:         2005:112799  CAPLUS
DOCUMENT NUMBER:          142:385283
TITLE:                    Antitumor effect of novel NF-κB inhibitor on
                          hormone-refractory prostate cancer
AUTHOR(S):                Kikuchi, Eiji
CORPORATE SOURCE:         School of Medicine, Dep. of Ulorogy, Keio University,
                          Japan
SOURCE:                   Keio Igaku (2004), 81(4), T261-T270
                          CODEN: KEIGAS; ISSN: 0368-5179
PUBLISHER:                Keio Igakkai
DOCUMENT TYPE:            Journal
LANGUAGE:                 Japanese
AB   The novel NF-κB inhibitor dihydroxymethylepoxyquinomicin (DHMEQ)
     inhibited human hormone-refractory prostate cancer transplanted in nude
     mice by inhibiting DNA binding to NF-κB.
IT   287194-40-5, DHMEQ
     RL: DMA (Drug mechanism of action); THU (Therapeutic use); BIOL
     (Biological study); USES (Uses)
```

(antitumor effect of novel NF-κB inhibitor on hormone-refractory prostate cancer)

RN 287194-40-5 CAPLUS

CN Benzamide, 2-hydroxy-N-[(1S,2S,6S)-2-hydroxy-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L4 ANSWER 2 OF 21 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:12801 CAPLUS

DOCUMENT NUMBER: 142:273196

TITLE: Molecular target therapy of ATL by new NF-κB inhibitors

AUTHOR(S): Horie, Ryouichi

CORPORATE SOURCE: Fourth Department of Internal Medicine, School of Medicine, Kitasato University, Sagamihara, 228-8555, Japan

SOURCE: Ketsueki, Shuyoka (2004), 49(3), 257-265
CODEN: KETSBI; ISSN: 0915-8529

PUBLISHER: Kagaku Hyoronsha

DOCUMENT TYPE: Journal; General Review

LANGUAGE: Japanese

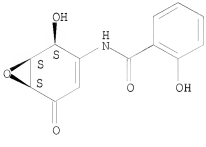
AB A review. Mol. target therapy of adult T cell leukemia/lymphoma (ATL) by new NF-κB inhibitors is reviewed including the role of NF-κB in the pathol. of ATL and the antileukemia mechanism of NF-κB inhibitors such as dehydroxymethylepoxyquinomicin (DHMEQ).

IT 287194-40-5, DHMEQ
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mol. target therapy of ATL by new NF-κB inhibitors)

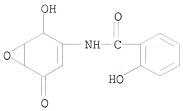
RN 287194-40-5 CAPLUS

CN Benzamide, 2-hydroxy-N-[(1S,2S,6S)-2-hydroxy-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L4 ANSWER 3 OF 21 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:975663 CAPLUS
DOCUMENT NUMBER: 142:253890
TITLE: Induction of thyroid cancer cell apoptosis by a novel nuclear factor κB inhibitor, dehydroxymethylepoxyquinomicin
AUTHOR(S): Starenki, Dmitriy V.; Namba, Hiroyuki; Saenko, Vladimir A.; Ohtsuru, Akira; Maeda, Shigeto; Umezawa, Kazuo; Yamashita, Shunichi
CORPORATE SOURCE: Department of Molecular Medicine, Atomic Bomb Disease Institute, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
SOURCE: Clinical Cancer Research (2004), 10(20), 6821-6829
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The objective of the study was to determine the effects of a novel selective nuclear factor κB (NF-κB) inhibitor, dehydroxymethylepoxyquinomicin (DHMEQ), in thyroid carcinoma cells in vitro and in vivo and to addnl. elucidate the mol. mechanisms underlying the action of this chemotherapeutic agent. In the in vitro expts., the induction of apoptosis by DHMEQ in various human thyroid carcinoma cell types was determined by flow cytometry anal. of annexin-V binding and the caspase activation by Western blotting. For the in vivo study, female nu/nu mice were xenografted with s.c. FRO thyroid tumors. DHMEQ solution was injected i.p. at a dose of 8 mg/kg/day for two weeks. Tumor dimensions were monitored twice weekly, and apoptosis in tumor specimens was determined by terminal deoxynucleotidyl transferase-mediated nick end labeling staining. Treatment with DHMEQ substantially inhibited the translocation of p65 and p50 NF-κB subunits to the nucleus, the DNA-binding activity of the RelA/p65, NF-κB-dependent expression of the inhibitor of apoptosis (IAP)-family proteins, cIAP-1, cIAP-2, and XIAP, and the de novo synthesis of inhibitor of nuclear factor κB α. At concentration levels ranging from 0.1 to 5 μg/mL, DHMEQ induced a caspase-mediated apoptotic response that could be abrogated by the c-Jun NH2-terminal kinase inhibitor SP600125 but not by either mitogen-activated protein/extracellular signal-regulated kinase kinase or p38 inhibitors. In contrast, normal human thyrocytes were resistant to DHMEQ-induced apoptosis. At higher doses of DHMEQ we observed the necrotic-like killing of both normal and malignant thyrocytes, which was resistant to mitogen-activated protein kinase inhibitors. In nude mice DHMEQ substantially inhibited tumor growth without observable side effects, and increased nos. of apoptotic cells were observed in the histol. sections of tumors treated with DHMEQ. Our results show the potential usefulness of the novel NF-κB inhibitor, DHMEQ, in future therapeutic strategies for the treatment of thyroid cancers that do not respond to conventional approaches.
IT 326499-51-8
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nuclear factor-κB inhibitor dehydroxymethylepoxyquinomicin inhibited growth and induced apoptosis in human thyroid carcinoma cell lines ARO, FRO, KTC-1, TPC-1, WRO, KTC-2 and in mouse injected with FRO cell line)
RN 326499-51-8 CAPLUS
CN Benzamide, 2-hydroxy-N-(2-hydroxy-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl)- (CA INDEX NAME)



REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 21 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:696362 CAPLUS
DOCUMENT NUMBER: 141:206963
TITLE: Dehydroxymethylepoxyquinomicin derivative (DHMEQ) and process for optical resolution thereof
INVENTOR(S): Umezawa, Kazuo; Kato, Kuniki; Suzuki, Yoshikazu; Horiguchi, Yutaka; Nakashima, Jun; Hata, Hiroyuki; Namba, Hiroyuki; Takei, Izumi; Horie, Ryouichi
PATENT ASSIGNEE(S): Keio University, Japan
SOURCE: PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004072056	A1	20040826	WO 2004-JP1623	20040216 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004210789	A1	20040826	AU 2004-210789	20040216 <--
CA 2515658	A1	20040826	CA 2004-2515658	20040216 <--
EP 1600445	A1	20051130	EP 2004-711505	20040216
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
CN 1774429	A	20060517	CN 2004-80009786	20040216
US 20060167086	A1	20060727	US 2005-545234	20050812

PRIORITY APPLN. INFO.:		
JP 2003-37167	A	20030214
JP 2003-39098	A	20030218
JP 2003-288281	A	20030806
WO 2004-JP1623	A	20040216

OTHER SOURCE(S): MARPAT 141:206963
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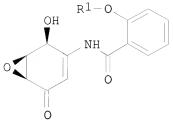


I

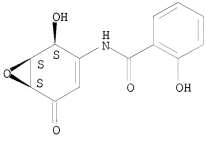
AB Title compds. I [R1 = H, alkanoyl] were disclosed. Optically pure (+)-, (−)-5-dehydroxymethylepoxyquinomicin C (DHM2EQ) were prepared from (±)-DHM2EQ. For example, (+)-, (−)-DHM2EQ were directly obtained by optical resolution with the use of the optically active column [DAICEL CHIRALPAK AD column (10 mm i.d. x 250 mm), column temperature:40 °C, mobile phase:acetic acid/methanol (0.5 volume/volume%), flow rate:1.0 mL/min]. In cell adhesion inhibition assays, the IC50 value of (−)-DHM2EQ was 0.64 μg/mL at a concentration of 10 ng/mL of TNF-α. Compds. I are claimed useful for the treatment of inflammation, tumor, etc.

IT 287194-38-1
RL: PAC (Pharmacological activity); PEP (Physical, engineering or chemical process); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(dehydroxymethylepoxyquinomicin derivative (DHMEQ) and process for optical resolution thereof)

RN 287194-38-1 CAPLUS

CN Benzamide, 2-hydroxy-N-[(1R,2R,6R)-2-hydroxy-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]-, rel- (CA INDEX NAME)

Relative stereochemistry.

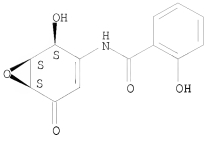


IT 287194-40-5P 287194-41-6P
RL: PAC (Pharmacological activity); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(dehydroxymethylepoxyquinomicin derivative (DHMEQ) and process for optical resolution thereof)

RN 287194-40-5 CAPLUS

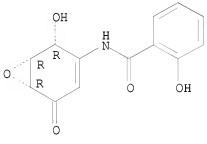
CN Benzamide, 2-hydroxy-N-[(1S,2S,6S)-2-hydroxy-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (−).

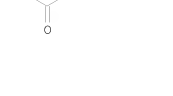


RN 287194-41-6 CAPLUS
CN Benzamide, 2-hydroxy-N-[(1R,2R,6R)-2-hydroxy-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L4 ANSWER 5 OF 21 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:581870 CAPLUS
DOCUMENT NUMBER: 141:277385
TITLE: Preparation and biological activities of optically active dehydroxymethylepoxyquinomicin, a novel NF-κB inhibitor
AUTHOR(S): Suzuki, Yoshikazu; Sugiyama, Chie; Ohno, Osamu; Umezawa, Kazuo
CORPORATE SOURCE: Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Kohoku-ku, Yokohama, 223-0061, Japan
SOURCE: Tetrahedron (2004), 60(33), 7061-7066
CODEN: TETRAB; ISSN: 0040-4020
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 141:277385
GI



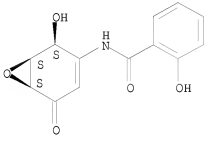
I

AB NF-κB is a transcription factor that induces inflammatory cytokines and anti-apoptotic proteins. We have designed a new NF-κB inhibitor based on the structure of the antibiotic epoxyquinomicin C. The designed compound, dehydroxymethylepoxyquinomicin (DHMEQ) I was synthesized as a racemic form from 2,5-dimethoxyaniline through 5 steps. Application of racemic DHMEQ onto the chiral column (Chiralpak AD) directly gave enantiomeric DHMEQ after purification (-)-DHMEQ was more potent than its enantiomer. (-)-DHMEQ was found to inhibit NF-κB activity and macrophage differentiation induced by 12-O-tetradecanoylphorbol-13-acetate (TPA) in human monocyte THP-1 cells.

IT 287194-40-5P 757194-41-5P
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation)
(preparation of dehydroxymethylepoxyquinomicin enantiomers and their ability to inhibit NF-κB activity and macrophage differentiation induced by TPA in human THP-1 cells)

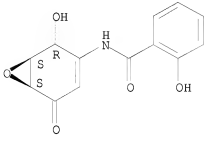
RN 287194-40-5 CAPLUS
CN Benzamide, 2-hydroxy-N-[(1S,2S,6S)-2-hydroxy-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 757194-41-5 CAPLUS
CN Benzamide, 2-hydroxy-N-[(1S,2R,6S)-2-hydroxy-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

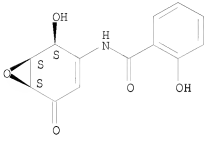


IT 287194-38-1P
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of dehydroxymethylepoxyquinomicin enantiomers and their ability to inhibit NF-κB activity and macrophage differentiation induced by TPA in human THP-1 cells)

RN 287194-38-1 CAPLUS

CN Benzamide, 2-hydroxy-N-[(1R,2R,6R)-2-hydroxy-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]-, rel- (CA INDEX NAME)

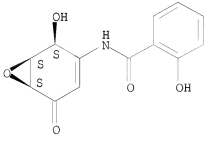
Relative stereochemistry.



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 21 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:168332 CAPLUS
DOCUMENT NUMBER: 141:64176
TITLE: Discovery, anti-inflammatory activity, and anticancer activity of a novel NF-κB inhibitor, DHMEQ
AUTHOR(S): Umezawa, Kazuo
CORPORATE SOURCE: Faculty of Science and Technology, Department of Applied Chemistry, Keio University, Yokohama, 223-0061, Japan
SOURCE: Igaku no Ayumi (2003), 207(12-13), 1008-1009
CODEN: IGAYAY; ISSN: 0039-2359
PUBLISHER: Ishiyaku Shuppan
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review, discussing the discovery, action mechanism, and clin. pharmacol. of a novel NF-κB inhibitor, DHMEQ, as antiinflammatory and anticancer agent.
IT 287194-40-5, DHMEQ
RL: DMA (Drug mechanism of action); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(discovery, action mechanism, and clin. pharmacol. of a novel NF-B inhibitor, DHMEQ, as antiinflammatory and anticancer agent)
RN 287194-40-5 CAPLUS
CN Benzamide, 2-hydroxy-N-[(1S,2S,6S)-2-hydroxy-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L4 ANSWER 7 OF 21 CAPLUS COPYRIGHT 2008 ACS on STN

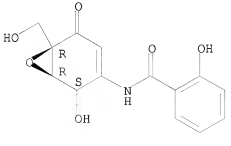
ACCESSION NUMBER: 2004:21398 CAPLUS
DOCUMENT NUMBER: 141:16586
TITLE: Antitumor effect of a novel nuclear factor-κB activation inhibitor in bladder cancer cells
AUTHOR(S): Horiguchi, Yutaka; Kuroda, Kenji; Nakashima, Jun; Murai, Masaru; Umezawa, Kazuo
CORPORATE SOURCE: Department of Urology, Keio University School of Medicine, Tokyo, 160-8582, Japan
SOURCE: Expert Review of Anticancer Therapy (2003), 3(6), 793-798
CODEN: ERATBJ; ISSN: 1473-7140
PUBLISHER: Future Drugs Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Nuclear factor (NF)-κB is a transcription factor that not only induces and controls various genes, including those of inflammatory cytokines, but also activates genes which suppress apoptosis. It has been clearly demonstrated that certain advanced human bladder cancer cells constitutively acquire the ability to activate NF-κB, which not only protects cancer cells from apoptotic cell death, but also upregulates the production of various cytokines that may increase the malignant potential of the disease and cause paraneoplastic syndromes. The NF-κB inhibitors may therefore be useful as anticancer agents. An NF-κB function inhibitor, a dehydroxymethyl derivative of epoxyquinomicin C (DHMEQ), has recently been designed and synthesized. The effectiveness of DHMEQ against advanced human bladder cancer cell line KU-19-19, in which NF-κB is constitutively activated, has been investigated. The DNA-binding activity of NF-κB was completely inhibited following 2-6-h exposure to 10 μg/mL of DHMEQ. Marked levels of apoptosis were observed 48 h after DHMEQ administration. These results confirmed that NF-κB activation maintains the viability of KU-19-19 cells, that DHMEQ inhibited constitutively activated NF-κB, and, consequently, apoptosis was induced. However, it was still possible that DHMEQ caused apoptotic cell death through some other mechanism which has not yet been fully investigated. The authors conclude that DHMEQ could represent a new treatment strategy against advanced bladder cancer.

IT 200496-85-1D, Epoxyquinomicin C, 5-Dehydroxymethyl derivative 287194-40-5, Dhmeq
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor effect of novel nuclear factor-κB activation inhibitor in bladder cancer cells)

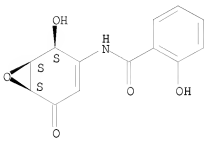
RN 200496-85-1 CAPLUS
CN Benzamide, 2-hydroxy-N-[(1R,2S,6R)-2-hydroxy-6-(hydroxymethyl)-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 287194-40-5 CAPLUS
CN Benzamide, 2-hydroxy-N-[(1S,2S,6S)-2-hydroxy-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 21 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:20478 CAPLUS
DOCUMENT NUMBER: 140:82263
TITLE: Drug composition containing NF-κb inhibitor
INVENTOR(S): Umezawa, Kazuo; Kawai, Yohko; Horie, Ryouichi; Watanabe, Toshiki; Toi, Masakazu; Matsumoto, Gaku; Horiguchi, Yutaka; Nakashima, Jun
PATENT ASSIGNEE(S): Keio University, Japan
SOURCE: PCT Int. Appl., 126 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004002465	A1	20040108	WO 2003-JP8134	20030626 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2500165	A1	20040108	CA 2003-2500165	20030626 <--
AU 2003244000	A1	20040119	AU 2003-244000	20030626 <--
EP 1541139	A1	20050615	EP 2003-736274	20030626
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
CN 1674881	A	20050928	CN 2003-814974	20030626
US 20060183794	A1	20060817	US 2005-519162	20050815
PRIORITY APPLN. INFO.:			JP 2002-185866 A	20020626
			JP 2003-37167 A	20030214
			WO 2003-JP8134 W	20030626

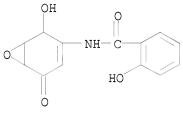
OTHER SOURCE(S): MARPAT 140:82263
AB Disclosed is a drug composition for ameliorating the symptoms attributed to

tumor cells, comprising an epoxyquinomicin derivative or a pharmaceutically acceptable salt thereof as an active ingredient. The inhibitory effect of 5,6-Epoxy-4-hydroxy-3-salicyloylamide-2-cyclohexenone (DHM2EQ) on NH-κb activity in adult T-cell leukemia (ATL) cells was examined

IT 326499-51-8
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug composition containing NF-κb inhibitor for ameliorating symptoms attributed to tumor cells)

RN 326499-51-8 CAPLUS

CN Benzamide, 2-hydroxy-N-(2-hydroxy-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl)- (CA INDEX NAME)



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 21 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:607117 CAPLUS

DOCUMENT NUMBER: 140:321129

TITLE: Preparation of radioactively labeled dehydroxymethylepoxyquinomicin, an NF-.vkappa.B function inhibitor

AUTHOR(S): Chaicharoenpong, C.; Kato, K.; Umezawa, K.

CORPORATE SOURCE: Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Yokohama, Japan

SOURCE: Drugs under Experimental and Clinical Research (2003), 29(1), 1-3
CODEN: DECRDP; ISSN: 0378-6501

PUBLISHER: Bioscience Ediprint Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

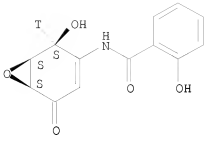
AB Dehydroxymethylepoxyquinomicin (DHMEQ), a synthetic derivative of epoxyquinomicin C, is a potent and specific inhibitor of NF-.vkappa.B in cultured cells. Tritium-labeled DHMEQ was synthesized with sodium borotritium. Specific radioactivity of the synthesized tritium-labeled DHMEQ was 15.45 mCi/mmol. This compound would be for the study of the mechanism of action and the stability of DHMEQ.

IT 677326-02-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of radioactively labeled dehydroxymethylepoxyquinomicin from 2,5-dimethoxyaniline)

RN 677326-02-2 CAPLUS

CN Benzamide, 2-hydroxy-N-[(1R,2R,6R)-2-hydroxy-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl-2-t]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 21 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2003:192226 CAPLUS
DOCUMENT NUMBER: 139:301538
TITLE: Novel Nuclear Factor κB Activation Inhibitor Prevents Inflammatory Injury in Unilateral Ureteral Obstruction
AUTHOR(S): Miyajima, Akira; Kosaka, Takeo; Seta, Kaori; Asano, Tomohiko; Umezawa, Kazuo; Hayakawa, Masamichi
CORPORATE SOURCE: Dep. Urol., Natl. Defense Med. College, Keio Univ., Yokohama, Kanagawa, Japan
SOURCE: Journal of Urology (Hagerstown, MD, United States) (2003), 169(4), 1559-1563
CODEN: JOURAA; ISSN: 0022-5347
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB PURPOSE We determined whether the novel nuclear factor κB activation inhibitor dehydroxymethylepoxyquinomicin (DHMEQ), which is derived from epoxyquinomicin C, affects renal inflammatory responses in unilateral ureteral obstruction. MATERIALS AND METHODS DHMEQ (8 mg./kg.) was administered to rats 1 day after unilateral ureteral obstruction and every day thereafter. Kidneys were harvested at day 7 after unilateral ureteral obstruction. Tissue nuclear factor κB activity and transforming growth factor-β were determined by electrophoretic mobility shift assay and bioassay using mink lung epithelial cells, resp. Renal tubular proliferation and apoptosis were detected by immunostaining proliferating cellular nuclear antigen and the TUNEL (Intergen, Purchase, New York) assay, resp. Leukocyte infiltration was detected by immunostaining for CD45. Fibrosis was assessed by measuring tissue hydroxyproline content. RESULTS Unilateral ureteral obstruction for 7 days significantly activated nuclear factor κB, induced tubular apoptosis, proliferation and interstitial fibrosis in the obstructed kidney of the control group compared with their unobstructed counterparts (30.3±4.5 nuclei per high power field vs. 1.7±0.4, 25.7±3.3 nuclei per high power field vs. 3.2±0.4 and 6.2±0.3 μmol. hydroxyproline per gm. tissue vs. 3.4±0.1, resp.). Conversely daily administration of DHMEQ (8 mg./kg.) significantly inhibited nuclear factor κB activation and decreased mean tubular apoptosis (9.5±2.1 nuclei per high power field), proliferation (10.2±2.4 nuclei per high power field) and interstitial fibrosis (4.9±0.4 μmol. hydroxyproline per gm. tissue) in the obstructed kidney. CONCLUSIONS Specific inhibition of nuclear factor κB can prevent inflammatory renal responses, suggesting that targeting nuclear factor κB activation may be feasible for preventing inflammatory kidney diseases.

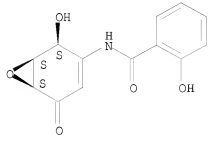
IT 287194-40-5, DHMEQ
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(novel nuclear factor κB activation inhibitor prevents inflammatory injury in unilateral ureteral obstruction)

RN 287194-40-5 CAPLUS

CN Benzamide, 2-hydroxy-N-[(1S,2S,6S)-2-hydroxy-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 21 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:39623 CAPLUS

DOCUMENT NUMBER: 139:127543

TITLE: Suppression of Hormone-refractory Prostate Cancer by a Novel Nuclear Factor κB Inhibitor in Nude Mice

AUTHOR(S): Kikuchi, Eiji; Horiguchi, Yutaka; Nakashima, Jun; Kuroda, Kenji; Oya, Mototsugu; Ohigashi, Takashi; Takahashi, Nozomu; Shima, Yutaka; Umezawa, Kazuo; Murai, Masaru

CORPORATE SOURCE: School of Medicine, Department of Urology, Keio University, Tokyo, 160-8582, Japan

SOURCE: Cancer Research (2003), 63(1), 107-110
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

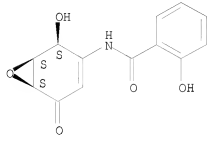
AB We have synthesized and explored the feasibility of using a novel nuclear factor (NF) κB inhibitor, a dehydroxymethylepoxyquinomicin designated as DHMEQ, against prostate cancer. The activity of NFκB, evaluated by transient transfection of a luciferase reporter DNA containing a specific binding sequence for NFκB, was inhibited by DHMEQ in three human hormone-refractory prostate cancer cell lines, DU145, JCA-1, and PC-3. Statistically significant growth inhibition was achieved by 20 μg/mL of DHMEQ, and marked levels of apoptosis were induced 48 h after DHMEQ administration in vitro. Electrophoretic mobility shift assay showed that DHMEQ completely inhibited NFκB DNA binding activity in JCA-1 cells. Furthermore, i.p. administrations of DHMEQ significantly inhibited pre-established JCA-1 s.c. tumor growth in nude mice without any side effects. Our result indicates the possibility of using a novel NFκB activation inhibitor, DHMEQ, as a new treatment strategy against hormone-refractory prostate cancer.

IT 287194-40-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(suppression of hormone-refractory prostate cancer by a novel nuclear factor κB inhibitor in nude mice)

RN 287194-40-5 CAPLUS

CN Benzamide, 2-hydroxy-N-[(1S,2S,6S)-2-hydroxy-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]- (CA INDEX NAME)

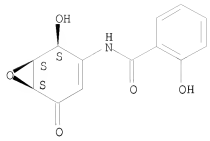
Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 21 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:942095 CAPLUS
DOCUMENT NUMBER: 138:395207
TITLE: Molecular design and biological activities of NF-κB inhibitors
AUTHOR(S): Umezawa, Kazuo; Chaicharoenpong, Chanya
CORPORATE SOURCE: Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Yokohama, 223-0061, Japan
SOURCE: Molecules and Cells (2002), 14(2), 163-167
CODEN: MOCEEK; ISSN: 1016-8478
PUBLISHER: Springer-Verlag Singapore Pte. Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. NF-κB is a transcription factor that induces inflammatory cytokines and anti-apoptotic proteins. We designed a new NF-κB inhibitor that is based on the structure of the antibiotic epoxyquinomicin C. The designed compound, dehydroxymethyl-epoxyquinomicin (DHMEQ), inhibited the TNF-α-induced activation of NF-κB, and showed an anti-arthritic effect in mice. Recently, we looked into its mechanism of inhibition. DHMEQ inhibited the TNF-α-induced cellular DNA binding of nuclear NF-κB, but not the phosphorylation or degradation of I-κB. Moreover, DHMEQ inhibited the TNF-α-induced nuclear accumulation of p65, a component of NF-κB. DHMEQ did not inhibit the nuclear transport of Smad2 and the large T antigen. Also, it did not inhibit the TNF-α-induced activation of JNK, but synergistically induced apoptosis with TNF-α in human T cell leukemia Jurkat cells. Therefore, DHMEQ specifically inhibited the NF-κB-activating pathway in the TNF-α-treated cells. Taken together, our data show that DHMEQ is a unique inhibitor of NF-κB that acts at the level of the nuclear translocation. It may be useful as an anti-inflammatory and anticancer agent.
IT 287194-40-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(design and activities of NF-κB inhibitors)
RN 287194-40-5 CAPLUS
CN Benzamide, 2-hydroxy-N-[(1S,2S,6S)-2-hydroxy-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



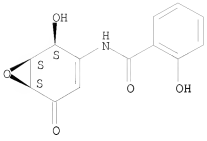
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 21 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:537262 CAPLUS
DOCUMENT NUMBER: 138:130755
TITLE: Inhibition of tumor necrosis factor-α-induced nuclear translocation and activation of NF-κB by dehydroxymethylepoxyquinomicin
AUTHOR(S): Ariga, Akiko; Namekawa, Jun-Ichi; Matsumoto, Naoki; Inoue, Jun-Ichiro; Umezawa, Kazuo
CORPORATE SOURCE: Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Yokohama, 223-0061, Japan
SOURCE: Journal of Biological Chemistry (2002), 277(27), 24625-24630
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We previously designed and synthesized an NF-κB inhibitor, dehydroxymethylepoxyquinomicin (DHMEQ), that showed anti-inflammatory activity in vivo. In the present study we looked into its mechanism of inhibition. DHMEQ inhibited tumor necrosis factor-α (TNF-α)- and 12-O-tetradecanoylphorbol-13-acetate-induced transcriptional activity of NF-κB in human T cell leukemia Jurkat cells. It also inhibited the TNF-α-induced DNA binding of nuclear NF-κB but not the phosphorylation and degradation of IκB. Moreover, DHMEQ inhibited the TNF-α-induced nuclear accumulation of p65, a component of NF-κB. It also inhibited TNF-α-induced nuclear transport of green fluorescent protein-tagged p65. On the other hand, DHMEQ did not inhibit the nuclear transport of Smad2 and large T antigen. Also, it did not inhibit TNF-α-induced activation of JNK but synergistically induced apoptosis with TNF-α in Jurkat cells. Taken together, these data indicate that DHMEQ is a unique inhibitor of NF-κB acting at the level of nuclear translocation.

IT 287194-40-5
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dehydroxymethylepoxyquinomicin inhibition of TNF-α-induced nuclear translocation and activation of NF-κB)
RN 287194-40-5 CAPLUS
CN Benzamide, 2-hydroxy-N-[(1S,2S,6S)-2-hydroxy-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 21 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:137177 CAPLUS
DOCUMENT NUMBER: 134:178457
TITLE: Preparation of salicylamide derivatives as anti-inflammatory and immunosuppressive agents and a process for preparation thereof
INVENTOR(S): Takeuchi, Tomio; Umezawa, Kazuo; To-e, Sakino; Matsumoto, Naoki; Sawa, Tsutomu; Yoshioka, Takeo; Agata, Naoki; Hirano, Shin-ichi; Isshiki, Kunio
PATENT ASSIGNEE(S): Mercian Corporation, Japan; Zaidan Hojin Biseibutsu Kagaku Kenkyu Kai
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001012588	A1	20010222	WO 2000-JP5332	20000809 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2393883	A1	20010222	CA 2000-2393883	20000809 <--
EP 1219596	A1	20020703	EP 2000-951914	20000809 <--
EP 1219596	B1	20061102		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
AT 344234	T	20061115	AT 2000-951914	20000809
AU 2000064727	A	20010313	AU 2000-64727	20000825 <--
US 6566394	B1	20030520	US 2002-49158	20020530 <--
PRIORITY APPLN. INFO.:			JP 1999-227389 A	19990811
			WO 2000-JP5332 W	20000809

OTHER SOURCE(S): MARPAT 134:178457
GI

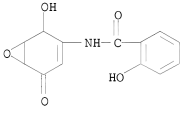
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Salicylamide derivs. and intermediates thereof represented by formulas (I; R1 = H, C2-4 alkanoyl; R2 = Q, Q1, Q2, Q3, Q4, Q5, Q6; wherein R3 = C1-4 alkyl), in particular II and III, are prepared Also described are drugs containing II or III as the active ingredient. The salicylamide derivs. represented by formulas II and III are useful as anti-inflammatory agents and immunosuppressive agents which exert an effect of inhibiting the activation of NF-κB with little side effects. Thus, 2,5-dimethoxyaniline was condensed with O-acetylsalicyloyl chloride in pyridine and EtOAc at room temperature for 30 min to give N-(2-acetoxybenzoyl)-2,5-dimethoxyaniline which was stirred with diacetoxyiodobenzene in MeOH at room temperature for 1 h to give 3-(O-acetylsalicylamido)-4,4-dimethoxy-2,5-cyclohexadienone in 50% yield for 2 steps. The latter compound was epoxidized by a mixture of 30% H2O2 and 1 N NaOH in THF under ice-cooling for 2 h to give 53% 5,6-epoxy-4,4-dimethoxy-3-salicylamido-2-cyclohexenone which was treated with Et2O.BF3 in CH2Cl2 under ice-cooling to give 47% 5,6-epoxy-2-salicylamido-2-cyclohexene-1,4-dione. The latter compound was reduced by NaBH4 in MeOH under ice-cooling for 10 min to give 72% II. II and III in vitro inhibited the production of NF-κB in a luciferase reporter gene assay and in vivo inhibited collagen-induced arthritis in mice.

IT 326499-51-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of salicylamide derivs. as anti-inflammatory and immunosuppressive agents)

RN 326499-51-8 CAPLUS

CN Benzamide, 2-hydroxy-N-(2-hydroxy-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl)- (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 21 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER:	2000:477042 CAPLUS
DOCUMENT NUMBER:	133:159622
TITLE:	Inhibition of rat embryo histidine decarboxylase by epoxyquinomicins
AUTHOR(S):	Matsumoto, Naoki; Agata, Naoki; Kuboki, Hiroshi; Iinuma, Hironobu; Sawa, Tsutomu; Takeuchi, Tomio; Umezawa, Kazuo
CORPORATE SOURCE:	Institute of Microbial Chemistry, Tokyo, 141-0021, Japan
SOURCE:	Journal of Antibiotics (2000), 53(6), 637-639 CODEN: JANTAJ; ISSN: 0021-8820
PUBLISHER:	Japan Antibiotics Research Association
DOCUMENT TYPE:	Journal

LANGUAGE: English

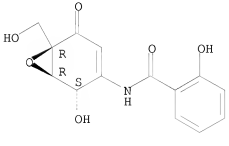
AB Epoxyquinomicins A, B, C, and D were first isolated from Amycolatopsis sp. as weak antibiotics. Studies on their biol activities revealed that these compds. inhibited type II collagen-induced arthritis. It was also found that these compds. showed low acute toxicity. Therefore, these epoxyquinomicins are unique candidates for antiinflammatory agents with the mode of action different from NSAIDs. Histidine decarboxylase is considered to be involved in the mechanism of inflammation by producing histamine. Lecanoric acid was isolated from a fungus as a histidine decarboxylase inhibitor. In view of the structural similarity between epoxyquinomicins and peptide-type lecanoric acid analogs, the authors studied the inhibition of histidine decarboxylase by epoxyquinomicins.

IT 200496-85-1, Epoxyquinomicin C 200496-86-2, Epoxyquinomicin D
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of rat embryo histidine decarboxylase by epoxyquinomicins)

RN 200496-85-1 CAPLUS

CN Benzamide, 2-hydroxy-N-[(1R,2S,6R)-2-hydroxy-6-(hydroxymethyl)-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]- (CA INDEX NAME)

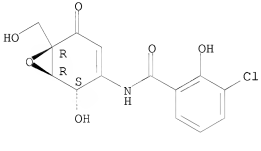
Absolute stereochemistry. Rotation (+).



RN 200496-86-2 CAPLUS

CN Benzamide, 3-chloro-2-hydroxy-N-[(1R,2S,6R)-2-hydroxy-6-(hydroxymethyl)-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 21 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2000:380057 CAPLUS
DOCUMENT NUMBER: 133:150385
TITLE: Synthesis of NF-κB activation inhibitors derived

from epoxyquinomicin C

AUTHOR(S): Matsumoto, Naoki; Ariga, Akiko; To-E, Sakino; Nakamura, Hikaru; Agata, Naoki; Hirano, Shin-Ichi; Inoue, Jun-Ichiro; Umezawa, Kazuo

CORPORATE SOURCE: Institute of Microbial Chemistry, Tokyo, 141-0021, Japan

SOURCE: Bioorganic & Medicinal Chemistry Letters (2000), 10(9), 865-869
CODEN: BMCLE8; ISSN: 0960-894X

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

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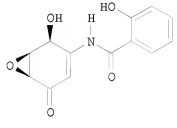

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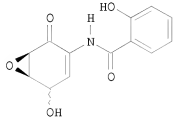


II

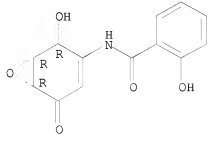
AB Regioisomeric dehydroxymethyl epoxyquinomicin C derivs., DHM2EQ (I) and DHM3EQ (II), were synthesized as new inhibitors of NF-κB activation. I and II were synthesized from 2,5-dimethoxyaniline in five steps. Since I was more active and less toxic than II, its stereochem. configuration was determined by X-ray crystallog. anal. Each enantiomer of the protected I was separated by a chiral column and deprotected. I inhibited TNF-α-induced activation of NF-κB in human T cell leukemia cells, and also inhibited collagen-induced arthritis in a rheumatoid model in mice.

IT 287194-41-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn, resolution and biol. activity of dehydroxymethyl derivs. of epoxyquinomicin C as NF-κB activation inhibitors)

RN 287194-41-6 CAPLUS

CN Benzamide, 2-hydroxy-N-[(1R,2R,6R)-2-hydroxy-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]- (CA INDEX NAME)

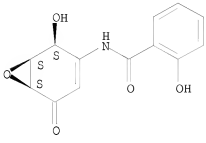
Absolute stereochemistry. Rotation (+).



IT 287194-40-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

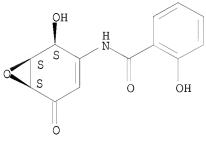
study, unclassified); PUR (Purification or recovery); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn, resolution and biol. activity of dehydroxymethyl derivs. of epoxyquinomicin C as NF-κB activation inhibitors)
RN 287194-40-5 CAPLUS
CN Benzamide, 2-hydroxy-N-[(1S,2S,6S)-2-hydroxy-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT 287194-38-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(prepn, resolution and biol. activity of dehydroxymethyl derivs. of epoxyquinomicin C as NF-κB activation inhibitors)
RN 287194-38-1 CAPLUS
CN Benzamide, 2-hydroxy-N-[(1R,2R,6R)-2-hydroxy-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]-, rel- (CA INDEX NAME)

Relative stereochemistry.



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 17 OF 21 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1999:282485 CAPLUS
DOCUMENT NUMBER: 131:129787
TITLE: Epoxyquinomicins: isolation, structure determination and synthetic studies
AUTHOR(S): Matsumoto, N.; Tsuchida, T.; Umekita, M.; Sawa, R.; Nakamura, H.; Iinuma, H.; Naganawa, H.; Sawa, T.; Hamada, M.; Takeuchi, T.; Ishizuka, M.; Hirano, S.; Yoshioka, T.
CORPORATE SOURCE: Institute of Microbial Chemistry, Japan
SOURCE: Tennen Yuki Kagobutsu Toronkai Koen Yoshishu (1997), 39th, 613-618

CODEN: TYKYDS
PUBLISHER: Nippon Kagakkai
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

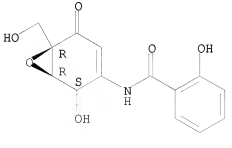
AB In the course of their screening program for novel antibiotics, the authors have isolated epoxyquinomicins A, B, C and D from the culture broth of Amycolatopsis sp. MK299-95F4. Epoxyquinomicins A and B showed weak antimicrobial activity against gram pos. bacteria and cytotoxicity at the concentration of epoxyquinomicin B .apprx. 18 μg/mL. Epoxyquinomicin C and D showed almost no antimicrobial activity and no cytotoxicity at the concentration of 100 μ g/mL. On the other hand, these antibiotics exhibited the improvement of collagen induced arthritis in vivo. The fermentation was carried out for 4 days with a medium consisting of glycerol, dextrin, Bacto-soytone, yeast extract and some inorg. salts. Bu acetate extract of broth supernatant (1.8 L) was concentrated, then purified by silica gel column chromatog. to give pure epoxyquinomicin A (18 mg), B (19 mg), C (44 mg) and D (77 mg). The structure of epoxyquinomicin A was examined first. The mol. formula C14H10NO6Cl was determined by HRFAB-MS. The structure of epoxyquinomicin A was deduced by various NMR spectral analyses including 1H-NMR, 13C-NMR, 1H-1H COSY, HMQC and HMBC. X-Ray crystallog. of epoxyquinomicin A supported this structure in addition to absolute stereochem. Thus, 1 was determined to be (5R,6S)-2-(3-chloro-2-hydroxybenzoylamino)-5-hydroxymethyl-5,6-epoxy-2-cyclohexene-1,4-dione. Epoxyquinomicin B was elucidated to be dechlorinated derivative of epoxyquinomicin A by comparison of the spectral data of epoxyquinomicin B with those of epoxyquinomicin A. The differences in the mol. formula, 1H- and 13C-NMR spectra between epoxyquinomicin A and D suggested that epoxyquinomicin D possessed a hydroxyl group at C-1 position instead of keto group in 1. The trans orientation between C-1 hydroxy group and epoxy ring was determined by x-ray anal. In the same manner, epoxyquinomicin C was determined to be dechlorinated derivative of epoxyquinomicin D. Epoxyquinomicins have unique structures which can be easily oxidized. So the authors investigated the total synthesis of these compds. They were successful in obtaining (±)-epoxyquinomicin B in 11% total yield from 3-hydroxy-4-nitrobenzaldehyde in efficiently in just 8 steps. Enantiomeric synthesis is now being further investigated.

IT 200496-85-1P, Epoxyquinomicin C 200496-86-2P, Epoxyquinomicin D
RL: BPN (Biosynthetic preparation); PRP (Properties); BIOL (Biological study); PREP (Preparation)
(isolation, structure determination and synthetic studies of epoxiquinomicins)

RN 200496-85-1 CAPLUS

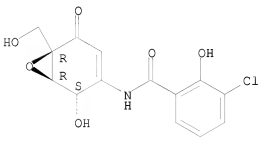
CN Benzamide, 2-hydroxy-N-[(1R,2S,6R)-2-hydroxy-6-(hydroxymethyl)-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 200496-86-2 CAPLUS
CN Benzamide, 3-chloro-2-hydroxy-N-[(1R,2S,6R)-2-hydroxy-6-(hydroxymethyl)-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]- (CA INDEX NAME)

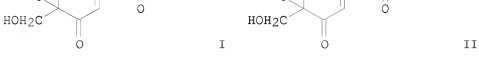
Absolute stereochemistry. Rotation (+).



L4 ANSWER 18 OF 21 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1998:112699 CAPLUS
DOCUMENT NUMBER: 128:166437
ORIGINAL REFERENCE NO.: 128:32803a,32806a
TITLE: Epoxyquinomicin C and D, their manufacture with Amycolatopsis species, and antirheumatic agents containing the antibiotics
INVENTOR(S): Takeuchi, Tomio; Tsuchita, Toshio; Nakamura, Hikaru; Iinuma, Takenobu; Sawa, Isao; Naganawa, Hiroshi; Hamada, Masashi; Hirano, Shinichi; Matsumoto, Naoki; Ishizuka, Masaaki
PATENT ASSIGNEE(S): Microbiochemical Research Foundation, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 15 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 10045738	A	19980217	JP 1996-199249	19960729 <--
PRIORITY APPLN. INFO.:			JP 1996-199249	19960729

GI



I II

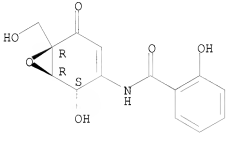
AB Epoxyquinomicin C [I (R = H)] and/or epoxyquinomicin D [I (R = Cl)] are manufactured by cultivation of Amycolatopsis sp. capable of producing the antibiotics. Antirheumatic agents contain epoxyquinomicin A [II (R =

Cl)], B [II (R = H)], C, D, and/or their salts as active ingredients. Amycolatopsis sp. MK299-95F4 was shake-cultured in a medium containing glycerin, dextrin, yeast extract, etc., at 27° for 4 days to produce epoxyquinomicin A, B, C, and D. Epoxyquinomicin A, B, and C strongly suppressed collagen-induced arthritis in mice.

IT 200496-85-1P, Epoxyquinomicin C 200496-86-2P, Epoxyquinomicin D
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BMF (Bioindustrial manufacture); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(manufacture of epoxyquinomicins with Amycolatopsis sp. for antirheumatic agents)

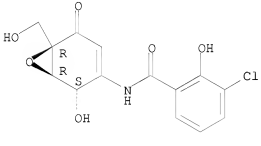
RN 200496-85-1 CAPLUS
CN Benzamide, 2-hydroxy-N-[(1R,2S,6R)-2-hydroxy-6-(hydroxymethyl)-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 200496-86-2 CAPLUS
CN Benzamide, 3-chloro-2-hydroxy-N-[(1R,2S,6R)-2-hydroxy-6-(hydroxymethyl)-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]- (CA INDEX NAME)

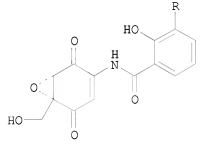
Absolute stereochemistry. Rotation (+).



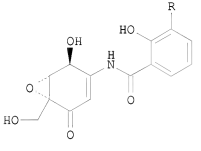
L4 ANSWER 19 OF 21 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER:	1997:771477 CAPLUS
DOCUMENT NUMBER:	128:72713
ORIGINAL REFERENCE NO.:	128:14139a,14142a
TITLE:	Epoxyquinomicins A, B, C and D, new antibiotics from Amycolatopsis. III. Physico-chemical properties and structure determination
AUTHOR(S):	Matsumoto, Naoki; Tsuchida, Toshio; Sawa, Ryuichi; Iinuma, Hironobu; Nakamura, Hikaru; Naganawa, Hiroshi; Sawa, Tsutomu; Takeuchi, Tomio

CORPORATE SOURCE: Institute of Microbial Chemistry, Tokyo, 141, Japan
SOURCE: Journal of Antibiotics (1997), 50(11), 912-915
CODEN: JANTAJ; ISSN: 0021-8820
PUBLISHER: Japan Antibiotics Research Association
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



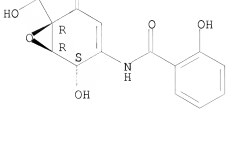
I R=Cl
II R=H



III R=H
IV R=Cl

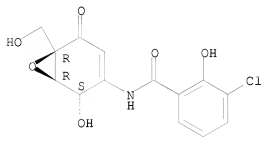
AB The structures of epoxyquinomicins A (I), B (II), C (III) and D (IV) were determined by spectroscopic studies. I was determined to be (5R,6S)-2-(3-chloro-2-hydroxybenzoylamino)-5-hydroxymethyl-5,6-epoxy-2-cyclohexene-1,4-dione. II was revealed to be the dechlorinated derivative of I. III and IV were determined to be the reduced derivative of II and I resp.
IT 200496-85-1 200496-86-2
RL: PRP (Properties)
(physicochem. properties and structure determination of epoxyquinomicins A, B,
C, and D, new antibiotics from Amycolatopsis)
RN 200496-85-1 CAPLUS
CN Benzamide, 2-hydroxy-N-[(1R,2S,6R)-2-hydroxy-6-(hydroxymethyl)-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 200496-86-2 CAPLUS
CN Benzamide, 3-chloro-2-hydroxy-N-[(1R,2S,6R)-2-hydroxy-6-(hydroxymethyl)-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]- (CA INDEX NAME)

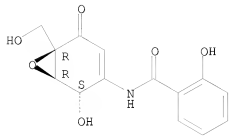
Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

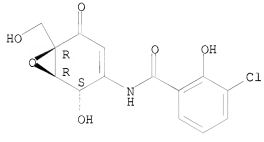
L4 ANSWER 20 OF 21 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1997:771476 CAPLUS
DOCUMENT NUMBER: 128:97457
ORIGINAL REFERENCE NO.: 128:18909a,18912a
TITLE: Epoxyquinomicins A, B, C and D, new antibiotics from Amycolatopsis II. Effect on type II collagen-induced arthritis in mice
AUTHOR(S): Matsumoto, Naoki; Iinuma, Hironobu; Sawa, Tsutomu; Takeuchi, Tomio; Hirano, Shin-Ichi; Yoshioka, Takeo; Ishizuka, Masaaki
CORPORATE SOURCE: Institute of Microbial Chemistry, Tokyo, 141, Japan
SOURCE: Journal of Antibiotics (1997), 50(11), 906-911
CODEN: JANTAJ; ISSN: 0021-8820
PUBLISHER: Japan Antibiotics Research Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The anti-arthritic effects of epoxyquinomicins on type II collagen-induced arthritis in DBA/1J mice were examined Prophylactic treatment with epoxyquinomicins A, B, C and D (1 .apprx. 4 mg/kg) had potent inhibitory effects on type II collagen-induced arthritis. In contrast to nonsteroidal anti-inflammatory drugs (NSAIDs), epoxyquinomicin C (1 .apprx. 30 mg/kg) had neither an anti-inflammatory effect on carrageenan-induced paw edema in rats nor an analgesic effect on acetic acid-induced writhing in mice. These results suggest that the mode of action of epoxyquinomicins is different from that of NSAIDs and that epoxyquinomicins may become useful drugs for the treatment of rheumatoid arthritis.
IT 200496-85-1, Epoxyquinomicin C 200496-86-2, Epoxyquinomicin D
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antirheumatic activity of epoxyquinomicins A, B, C and D in type II collagen-induced arthritis)
RN 200496-85-1 CAPLUS
CN Benzamide, 2-hydroxy-N-[(1R,2S,6R)-2-hydroxy-6-(hydroxymethyl)-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 200496-86-2 CAPLUS
CN Benzamide, 3-chloro-2-hydroxy-N-[(1R,2S,6R)-2-hydroxy-6-(hydroxymethyl)-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

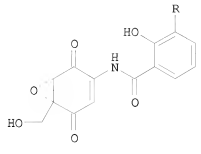


REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

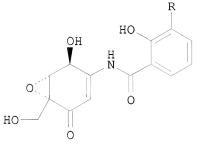
L4 ANSWER 21 OF 21 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER:	1997:771475 CAPLUS
DOCUMENT NUMBER:	128:72712
ORIGINAL REFERENCE NO.:	128:14139a,14142a
TITLE:	Epoxyquinomicins A, B, C and D, new antibiotics from Amycolatopsis I. Taxonomy, fermentation, isolation and antimicrobial activities
AUTHOR(S):	Matsumoto, Naoki; Tsuchida, Toshio; Umekita, Maya; Kinoshita, Naoko; Iinuma, Hironobu; Sawa, Tsutomu; Hamada, Masa; Takeuchi, Tomio
CORPORATE SOURCE:	Institute of Microbial Chemistry, Tokyo, 141, Japan
SOURCE:	Journal of Antibiotics (1997), 50(11), 900-905 CODEN: JANTAJ; ISSN: 0021-8820
PUBLISHER:	Japan Antibiotics Research Association
DOCUMENT TYPE:	Journal
LANGUAGE:	English

GI



I R=Cl
II R=H



III R=H
IV R=Cl

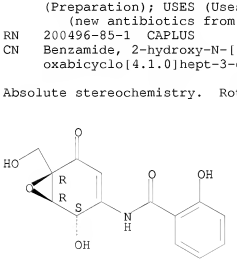
AB A new structural class of antibiotic, epoxyquinomicins A, B, C and D (I, II, III, and IV, resp.), were isolated from the culture broth of the strain MK299-95F4, which was related to Amycolatopsis sulphurea. Antimicrobial activity of I and II were weak against Gram-pos. bacteria, and III and IV showed almost no antimicrobial activity and no cytotoxicity. All these antibiotics showed improvement of collagen-induced arthritis in vivo.

IT 200496-85-1P, Epoxyquinomicin C 200496-86-2P, Epoxyquinomicin D
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); USES (Uses)
(new antibiotics from Amycolatopsis MK299-95F4)

RN 200496-85-1 CAPLUS

CN Benzamide, 2-hydroxy-N-[(1R,2S,6R)-2-hydroxy-6-(hydroxymethyl)-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]- (CA INDEX NAME)

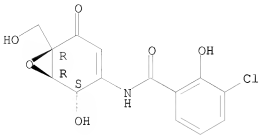
Absolute stereochemistry. Rotation (+).



RN 200496-86-2 CAPLUS

CN Benzamide, 3-chloro-2-hydroxy-N-[(1R,2S,6R)-2-hydroxy-6-(hydroxymethyl)-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT